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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/575,300 | EBERT ET AL. | |
| | Examiner | Art Unit | |
| | SEAN E. AEDER | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4-11,14,16 and 18-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-11, 14, 16, and 18-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/19/07; 3/26/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## *Detailed Action*

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/28/08 has been entered.

Claims 1, 2, 4-11, 14, 16, and 18-24 are pending.

Claims 1 and 24 have been amended by Applicant.

Claims 1, 2, 4-11, 14, 16, and 18-24 are currently under consideration.

## *Rejections Withdrawn*

The rejection under 35 U.S.C. 112, second paragraph, is withdrawn.

The rejection under 35 U.S.C. 112, first paragraph, for failing to comply with the restriction requirement, is withdrawn.

## *Response to Arguments*

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1, 2, 4-11, 14, 16, and 18-24 under 35 U.S.C. 112 first paragraph, for failing to comply with the enablement requirement, is maintained for the reasons stated in the Office Action of 5/17/07, the reasons stated in the Office Action of 10/19/08, the reasons stated in the Advisory Action of 1/29/08, and for the reasons set-forth below.

The Office Action of 10/19/08 contains the following text:

"While being enabling for a method of predicting survival of a patient with gastric cancer comprising (a) detecting MN/CA IX polypeptide in a sample comprising gastric cancer tissue, (b) quantitating the level of said MN/CA IX polypeptide in said sample, (c) comparing the level of MN/CA IX polypeptide of step (b) to the average level of MN/CA IX polypeptide in analogous samples from subjects with gastric cancer, (d) determining that said patient has a prognosis of shorter survival than the average subject with gastric cancer if the level of MN/CA IX polypeptide level of step (b) is higher than the average level of MN/CA IX polypeptide in analogous samples from subjects with gastric cancer, does not reasonably provide enablement for a method which is prognostic for every preneoplastic/neoplastic disease afflicting a subject vertebrate, wherein said disease affects a tissue, which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis, comprising (a) detecting MN/CA9 polypeptide in a preneoplastic/neoplastic tissue taken from said vertebrate, (b) quantitating the level of said MN/CA9 polypeptide in said sample, (c) comparing the level of MN/CA9 polypeptide of step (b) to the average level of MN/CA9 polypeptide in comparable samples taken from vertebrates afflicted by the same preneoplastic/neoplastic disease as the subject vertebrate, and (d) determining that said subject vertebrate has every type of poorer prognosis if the level of MN/CA9 polypeptide of step (b) is higher than the average level of MN/CA9 polypeptide in said comparable samples. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In the Reply of 8/16/07, Applicant states that the burden of proof is upon the Examiner to challenge a presumptive enabling disclosure and that no evidence has been presented as to why the methods would not work as claimed. Applicant further argues that the diagnostic expression patterns of MN/CA IX have been established, that MN/CA IX is not just a tumor marker but is implicated in the progression of different tumor types, and Tockman 1992 is inapposite, as it relates to establishing endpoints to identify whether a biomarker is *diagnostically* useful for a particular tumor, not whether or not an established tumor biomarker is useful *prognostically*. Applicant further states

that based on MN/CA IX's unique correlation with the presence of hypoxia and the value of hypoxia in cancer prognosis in a broad range of tumors, renewed expression of MN/CA IX in tumor cells could signify hypoxia or tumor progression and corresponding poorer prognosis in diseases similar to gastric cancer (see lines 21-27 of page 42). Applicant further argues that Examiner has not provided any evidence that suggests that the claimed prognostic methods would not work for just any type of prognosis of preneoplastic/neoplastic diseases of tissues, where MN/CA IX is normally expressed but its expression is lost or diminished upon carcinogenesis.

The amendments to the claims and the arguments found in the Reply of 8/16/07 have been carefully considered, but are not deemed to be persuasive in regards to being enabled for methods which uses expression levels of MN/CA IX to determine every type of prognosis for every preneoplastic/neoplastic disease afflicting a subject vertebrate, wherein said disease affects a tissue, which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis. In regards to the argument that no evidence has been presented as to why the methods would not work as claimed, the Office Action of 5/17/07 states that factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. These factors were addressed in the Office Action of 5/17/07, which demonstrates that undue experimentation would be required to determine with any predictability that the method would function as claimed.

The Office Action of 5/17/07 contains the following text addressing why it would require undue experimentation by one of skill in the art to determine, with any predictability, that the broadly claimed methods for using MN/CA IX expression levels to determine every type of prognosis of every preneoplastic/neoplastic disease afflicting a subject vertebrate, wherein said disease affects a tissue, which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis would function as claimed:

"The specification teaches a method which is prognostic for a patient with gastric cancer comprising (a) detecting MN/CA 9 polypeptide in a sample comprising tissue from .... gastric cancer, (b) quantitating the level of said MN/CA 9 polypeptide in said sample, (c) comparing the level of MN/CA 9 polypeptide of step (b) to the average level of MN/CA 9 polypeptide in analogous ... samples from subjects with gastric cancer, (d) determining that said patient has a prognosis of shorter survival than the average subject with gastric cancer if the level of MN/CA 9 polypeptide level of step (b) is higher than the average level of MN/CA 9 polypeptide in analogous ... samples from subjects with gastric cancer...(see Example 2, Example 3, and Figure 5, in particular).

The level of unpredictability for providing any type of prognosis for any type of disease is quite high. The state of the prior art dictates that if a molecule such as

MN/CA 9 polypeptide is to be used as a surrogate for a diseased state, some disease state must be identified in some way with the molecule. There must be some expression pattern in a particular tissue that would allow MN/CA 9 polypeptide to be used in a diagnostic or prognostic manner. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence of the polypeptide's expression in a particular tissue including the correlation to a diseased state, one of skill in the art would not be able to predictably use the polypeptide in any diagnostic or prognostic setting without undue experimentation.

Since neither the specification nor the prior art provide evidence of a universal association between the claimed method and … every type of preneoplastic/neoplastic disease afflicting a subject vertebrate, wherein said disease affects a tissue, which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis … every type of prognosis, a practitioner wishing to practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

Further, as noted in the written description rejection above, it is unclear which preneoplastic/neoplastic diseases affect a tissue which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis. Determining which preneoplastic/neoplastic diseases affect a tissue which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis would require undue experimentation.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method which is prognostic for every preneoplastic/neoplastic disease afflicting a subject vertebrate, wherein said disease

affects a tissue, which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis, comprising (a) detecting MN/CA9 polypeptide in just any sample comprising preneoplastic/neoplastic tissue taken from said vertebrate, (b) quantitating the level of said MN/CA9 polypeptide in said sample, (c) comparing the level of MN/CA9 polypeptide of step (b) to the average level of MN/CA9 polypeptide in just any "comparable" samples taken from vertebrates afflicted by the same preneoplastic/neoplastic disease as the subject vertebrate, and (d) determining that said subject vertebrate has every type of poorer prognosis if the level of MN/CA9 polypeptide of step (b) is higher than the average level of MN/CA9 polypeptide in said comparable samples, … and Applicant has not enabled said method because it has not been shown that detecting MN/CA9 polypeptide in just any sample comprising preneoplastic/neoplastic tissue taken from just any vertebrate with just any preneoplastic/neoplastic disease, wherein said disease affects a tissue, which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis, quantitating the level of said MN/CA9 polypeptide in said sample, comparing said level to the average level of MN/CA9 polypeptide in just any "comparable" samples taken from vertebrates afflicted by the same preneoplastic/neoplastic disease as the subject vertebrate, wherein said subject vertebrate has every type of poorer prognosis if the level of MN/CA9 polypeptide in the sample from said subject is higher than the average level of MN/CA9 polypeptide in said comparable samples...

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed."

In regards to arguments that diagnostic expression patterns have been established for MN/CA IX, the instant claims are not drawn to diagnosis.

In regards to the argument that Tockman 1992 is inapposite, as it relates to establishing endpoints to identify whether a biomarker is *diagnostically* useful for a particular tumor, not whether or not an established tumor biomarker is useful *prognostically*, Tockman 1992 teaches a method that is used to identify diagnostic *and* prognostic markers. Tockman et al teaches that prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). A particular prognosis is a disease end point that is obviously amenable to the methods taught by Tockman et al.

Further, in regards to the theory that renewed expression of MN/CA IX in tumor cells could signify hypoxia or tumor progression and corresponding poorer prognosis in diseases similar to gastric cancer (see lines 21-27 of page 42), the claimed methods are drawn to *prognostic* methods based on MN/CA IX expression. How MN/CA IX may affect tumor progression or a particular prognosis is not claimed. Further, the unpredictability of said theory is highlighted in Pastorekov and Zavada, which teaches that a subject with one cancer having a high MN/CA IX expression level would have the

*opposite* prognosis as a patient with a different cancer that has a high MN/CA IX expression (see left column of page 251, in particular).

In regards to the argument that Examiner has not provided any evidence that suggests that the claimed prognostic methods would not work for just any type of prognosis of preneoplastic/neoplastic diseases of tissues, where MN/CA IX is normally expressed but its expression is lost or diminished upon carcinogenesis, it is noted that the specification discloses that "prognosis" encompasses survival, disease recurrence, and response to treatment (see page 9, in particular). Determining (1) which preneoplastic/neoplastic diseases affect a tissue which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis and (2) determining whether expression levels of MN/CA IX correlate with survival, disease recurrence, and response to treatment in subjects with preneoplastic/neoplastic diseases that affect a tissue which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis would require undue experimentation."

In the Submission of 3/28/08, Applicant has amended claims 1 and 24 to recite specific tissues to be used in the claimed invention. Applicant states that such amendments would address any question of "undue experimentation" in regard to determining which tissues normally express MN/CA IX but lose or have significantly reduced MN/CA IX expression upon carcinogenesis. Further, Applicant argues that it is not every type of poorer prognosis and every end point that needs to be enabled for the instant claims. Applicant further argues that the Examiner is suggesting a standard for enablement where methods would have to be perfected after years of accumulated clinical data before filing to meet the enablement requirements and such a standard would not be in tune with the purpose recited in the U.S. constitution for granting patents. Applicant further argues that case law is clear that pioneer inventions are entitled to broad claim coverage and goals of the Constitution would not be served by refusing pioneer inventors Claims to contributions to cancer prognosis. Applicant further states that recognition by Applicants that MN/CA IX expression can be used for

prognosis in preneoplastic/neoplastic tissues that normally express MN/CA IX, but lose expression upon carcinogenesis, provides a benefit to the public as another option for cancer prognosis, and only relates to a limited number of tissues. Applicant further indicates that "comparable samples" of the claimed invention are not just "any samples"; rather, "comparable samples" are samples from a patient's tumor/metastatic lesion and/or tissues adjacent thereto. Applicant further states that various aspects of the invention are counterintuitive and once one of skill is privy to the counterintuitive aspects of the instant invention, routine methods of detecting the level of MN/CA IX expression and or selecting appropriate samples and comparable samples can be used. Applicant further states the instant application teaches numerous methods of how to make a comparison of MN/CA IX expression levels in, for example, a patient's tissue sample and a comparable normal sample. In regards to Tockman et al, Applicant argues that "population trials" are not required to validate disease end points and establishment of "disease end points" are not necessary for enablement under U.S. patent law. Applicant further argues that Tockman et al does not raise a "reason to doubt" to challenge a presumptively enabling disclosure. Applicant further states the cited portions of Tockman et al relate only to diagnostic methods and not generalized prognostic methods as claimed, and MN/CA IX has already been well established as a diagnostic marker. Applicant further states that there is no reason to doubt truth of statements relied upon for enabling support in the specification for the claimed invention. Applicant further argues that what is known in the art of cancer prognosis confirms that MN/CA IX would be expected by those of skill in the art to be a highly

predictable marker of multiple types of cancer prognosis, including “survival, risk of recurrence, and response to treatment". Applicant further states that for diseases of tissues in which MN/CA IX is not normally expressed MN/CA IX has been established as a potential indicator of every type of poor prognosis, whether the disease end point is survival, risk of recurrence or response to treatment. Applicant states that because of MN/CA IX’s close association with tumor hypoxia and tumor aggressiveness, one of skill in the art would expect that CA IX would correlate with several end points of prognosis. Applicant further cites Tatum et al (Int J Radiat Biol, 2006, 82(10): 699-757) and concludes that because of CA IX’s close association with tumor hypoxia, CA IX is uniquely suited as an expected to be a generalized tumor marker of several types of poor prognosis, such as "outcome, survival, and treatment response". Applicant further states that the Cancer Imaging Program of the National Cancer Institute would not consider the use of MN/CA IX as a generalized biomarker of different types of poor prognosis if they thought that its expression was unpredictable. Applicant further cites Potter and Harris (Cell Cycle, 2004, 3(2): 164-167) and states that studies referred to by Potter and Harris include findings that MN/CA IX expression correlated with poor survival and outcome after radiation therapy in carcinoma of the cervix, higher relapse rate and worse overall survival in invasive breast carcinoma, poor outcome and poor survival in nonsmall cell lung cancer, poor survival in nasopharyngeal carcinoma, and resistance of squamous cell head and neck cancer to chemotherapy. Applicant further states that the one exception to the rule of CA IX association with poor prognosis in tissue in which CA IX is not normally expressed is renal cell carcinoma, which is a

disease in which CA IX induction by hypoxia has been uncoupled with a genetic mutation in the VHL gene.

The amendments to the claims and the arguments found in the Submission of 3/28/08 have been carefully considered, but are not deemed persuasive. In regards to amendments to claims 1 and 24 to recite specific tissues to be used in the claimed invention and that such amendments would address any question of "undue experimentation" in regard to determining which tissues normally express MN/CA IX but lose or have significantly reduced MN/CA IX expression upon carcinogenesis, factors used to determine undue experimentation are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). In the broadly claimed invention, undue experimentation would be required even with recitation of which tissues are to be used in the claimed invention. For instance, the claims are broadly drawn to a method which is prognostic for every preneoplastic/neoplastic disease afflicting a subject vertebrate, wherein said disease affects a tissue, which

tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis, comprising (a) detecting MN/CA9 polypeptide in a preneoplastic/neoplastic tissue taken from said vertebrate, (b) quantitating the level of said MN/CA9 polypeptide in said sample, (c) comparing the level of MN/CA9 polypeptide of step (b) to the average level of MN/CA9 polypeptide in just any comparable sample taken from vertebrates afflicted by the same preneoplastic/neoplastic disease as the subject vertebrate, and (d) determining that said subject vertebrate has every type of poorer prognosis if the level of MN/CA9 polypeptide of step (b) is higher than the average level of MN/CA9 polypeptide in said comparable samples, wherein said affected tissue is selected from a group consisting of gastric mucosa, gallbladder, biliary ducts, ductal cells of the duodenal glands, testis, ovary, basal cells of hair follicles, and central nervous system choroid plexus. The nature of the invention is cancer prognosis based on expression of a particular biomarker that has not been shown to be prognostic as claimed for the diseases encompassed by the claims. The level of skill in the art and the direction provided by the inventor for merely detecting expression of MN/CA IX is high. The state of the prior art, as outlined by Tockman et al, is that using a particular expression of a particular biomarker as an indicator of a diseased state (in this case just any type of poor prognosis) is highly unpredictable without a demonstration that said particular expression of said particular biomarker indicates said diseased state. While Applicant provides a single working example of the claimed invention, said working example does not demonstrate the invention would predictably function as broadly claimed based on the unpredictability of

the art and what is known in the art. Since neither the specification nor the prior art provide evidence of a universal association between the claimed method and every type of preneoplastic/neoplastic disease afflicting a subject vertebrate, wherein said disease affects a tissue, which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis, and every type of poor prognosis, and using just any comparable sample taken from vertebrates afflicted by the same preneoplastic/neoplastic disease as the subject vertebrate, a practitioner wishing to practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

In regards to the arguments that it is not every type of poorer prognosis and every end point that needs to be enabled for the instant claims and that the Examiner is suggesting a standard for enablement where methods would have to be perfected after years of accumulated clinical data before filing to meet the enablement requirements and such a standard would not be in tune with the purpose recited in the U.S. constitution for granting patents, MPEP 2164 requires what is "defined by the claim(s)" needs to be enabled. Due to the undue experimentation discussed above, the scope of what is defined by the claims is not enabled. Further, it is noted that working examples do not have to be presented by Applicant before filling to meet the enablement requirements; rather, MPEP 2164.5 allows declarations demonstrating working examples to be presented after the filing date in order to demonstrate that a claimed invention actually works.

In regards to the argument that case law is clear that pioneer inventions are entitled to broad claim coverage and goals of the Constitution would not be served by refusing pioneer inventors Claims to contributions to cancer prognosis, broad claim coverage is given to enabled claims. The scope of the instant claims is not enabled for the reasons discussed above and below.

In regards to the argument that recognition by Applicants that MN/CA IX expression can be used for prognosis in preneoplastic/neoplastic tissues that normally express MN/CA IX, but lose expression upon carcinogenesis, provides a benefit to the public as another option for cancer prognosis, and only relates to a limited number of tissues, Applicant is arguing limitations not recited in the claims. The claims encompass methods wherein MN/CA IX expression is detected in any preneoplastic/neoplastic tissue from any preneoplastic/neoplastic disease afflicting a subject vertebrate wherein said disease affects a tissue which tissue normally expresses MN/CA IX, but lose expression upon carcinogenesis. Such affected tissue includes tissues affected by a disease that metastasizes to said tissue.

In regards to the argument that "comparable samples" are samples from a patient's tumor/metastatic lesion and/or tissues adjacent thereto, Applicant is arguing limitations not recited in the claims or required by the disclosure. Further, in regards to the argument that once one of skill is privy to the counterintuitive aspects of the instant invention, routine methods of detecting the level of MN/CA IX expression and or selecting appropriate samples and comparable samples can be used, the claims encompass methods of using just any sample as a "comparable sample".

In regards to the arguments related to Tockman et al and that "population trials" are not required to validate disease end points and establishment of "disease end points" are not necessary for enablement under U.S. patent law, Tockman et al is cited as a teaching that demonstrates that unpredictable state of the art and the state of the art for determining whether a particular biomarker is indicative of a particular disease state. Further, in regards to the argument that the cited portions of Tockman et al relate only to diagnostic methods and not generalized prognostic methods as claimed, and MN/CA IX has already been well established as a diagnostic marker, Tockman et al teaches a method that is used to identify diagnostic *and* prognostic markers. Tockman et al teaches that prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). A particular prognosis is a disease end point that is obviously amenable to the methods taught by Tockman et al. While Applicant provides a single working example of the claimed invention, said working example does not demonstrate the invention would predictably function as broadly claimed based on the unpredictability of the art and what is known in the art as taught by Tockman et al. In view of what is known in the art and the disclosed example, the unpredictability of the art taught by Tockman et al does raise a "reason to doubt" the breadth of the instant claims.

In regards to the argument that what is known in the art of cancer prognosis confirms that MN/CA IX would be expected by those of skill in the art to be a highly predictable marker of multiple types of cancer prognosis, including "survival, risk of

recurrence, and response to treatment", the Examiner disagrees. Even in light of what is known in the art of MN/CA IX, the unpredictability of the art and that lack of examples demonstrating the breadth of the claims would lead those of skill in the art to recognize that the invention could not predictably be performed in commensurate with the scope of the claims without undue experimentation.

In regards to the studies demonstrating an increase in MN/CA IX protein is indicative of a poor prognosis in tissues which do not normally express MN/CA IX but have increased MN/CA IX upon carcinogenesis, said examples are not within the scope of the instant claims. Further, in regards to renal cell carcinoma, wherein a decrease in MN/CA IX is indicative of a poor prognosis, such an example highlights the unpredictability of using a particular MN/CA IX expression as a marker of a particular prognosis without demonstrating said particular MN/CA IX expression correlates with said particular prognosis.

**Further**, the teachings of Matsumura et al (Neurol Med Chir, 1997, 37:916-919), Hicks et al (Urol Int, 2003, 70(3):247-8), Young et al (Int J Gynecol Pathol, 1992, 11(2):96-104), and Ishizawa et al (Asian Journal of Surgery, July 2006, 29(3):145-148) provide evidence why the instant invention is not enabled in commensurate with the scope of the claims. Each of said teachings demonstrate methods wherein renal cell carcinoma *affects* a tissue (gallbladder tissue, ovary tissue, testis tissue, or central nervous system choroid plexus) which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis (see abstract of each teaching in view of Table 4 of Ivanov et al (American Journal of

Pathology, 158(3): 905-19). Further, the instant specification discloses that MN/CA IX is expressed at lower levels in patient samples from renal cell carcinoma patients with poorer prognosis, as compared to the expression of MN/CA IX in comparable samples from patients afflicted with renal cell carcinoma with a better prognosis. Therefore, in view of the specification, Ivanov et al, and Matsumura et al, Hicks et al, Young et al, or Ishizawa et al, a method is supported which is prognostic for a preneoplastic/neoplastic disease (renal cell carcinoma) afflicting a subject vertebrate, wherein said disease affects a tissue (gallbladder tissue, ovary tissue, testis tissue, or central nervous system choroid plexus) which normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis, said method comprising: (a) detecting MN/CA IX protein in a sample comprising preneoplastic/neoplastic tissue (renal cell carcinoma tissue) taken from said vertebrate, (b) quantitating the lever of said MN/CA IX protein in said sample, (c) comparing the level of MN/CA IX protein of step (b) to the average level of MN/CA IX protein in comparable samples taken from vertebrates afflicted by the same preneoplastic /neoplastic disease as the subject vertebrate, and (d) determining that said subject vertebrate has a poorer prognosis if the level of MN/CA IX protein of step (b) is **lower** than the average level of MN/CA IX protein in said comparable samples, than if said MN/CA IX protein of step (b) were at a higher level in said sample relative to said average level, wherein said tissue is selected from the group consisting of gastric mucosa, gallbladder, biliary ducts, ductal cells of duodenal glands, testis including ductular efferens and rete testis, ovary including surface coelomic epithelium and rete

ovari, basal cells of hair follicles, and centratl nervous system choroid plexus. This method, supported by the specification, Ivanov et al, and Matsumura et al, Hicks et al, Young et al, or Ishizawa et al, provides another reason why that the claimed invention cannot be practiced in commensurate with the scope of the claims with an expectation of success.

## *Summary*

No claim is allowed.

## *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Sean E Aeder/
Examiner, Art Unit 1642